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EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,903	SVANBORG ET AL.	
	Examiner	Art Unit	
	Agnes B. Rooke	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,18-21 and 23-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 18-21, 23-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Final action is in response to the paper file on 10/29/2007.

The amendments submitted on 10/29/2007 are acknowledged.

Status of Claims

Claims 1-14, 18-21, and 23-35 are pending and under consideration. New claims are 26-35. Cancelled claims are 15-17 and 22.

All rejections no present in this office action are withdrawn in view of the amendments to the claims

New Objections and Rejections Necessitated by Amendments

Objections to Claims

Claims are objected to for the following informalities:

(a) Claims 1, 4, 7, 29, 31-35 are objected to because the proper naming of sequences is SEQ ID NO:1, for example.

(b) In claim 5, line 4, the additional space should be deleted.

(c) In claims 8, 11, and 12, the naming of an alpha-lactalbumin should be constant since Applicants use the "alpha" term and the alpha symbol interchangeably.

Corrections of the above are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 18-21, and 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, Applicants refer to a phrase that the cofactor is an unsaturated fatty acid has "a configuration similar to C18:1:9 or C18:1:11 with the proviso that the cofactor is not C18:1:9." Examiner finds the claim indefinite because it is not certain what is the specific structure of fatty acids that are similar to C18:1:9 but still different than C18:1:9, therefore the claim is indefinite, Since the fatty acids are not distinctly claimed as it is required. All dependent claims are included in the instant rejection because they do not cure the deficiencies of the base claim.

In claim 2, Applicants claim that the cofactor "has a stero-specificity similar to cis C18:1:9 and cis C18:1:11 fatty acid." Examiner finds this claim indefinite because the stereospecificity describes a reaction that necessarily yields a given stereoisomer because of the mechanism of the reaction and thus the stereospecificity always yields of a particular stereoisomer. Thus, in the instant case, a cofactor of undefined structure that has a characteristic that is similar to C18:1:9, for example, would not necessarily have the same stereo-specificity as the cis C18:1:9. Therefore, further specification of such cofactor(s) is required in the claim as presented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 18-21, and 23-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

In claims 1 and 2, Applicants present a new matter because there is no support in the disclosure, as originally filed of the phrases: in claim 1: "configuration similar to" and in claim 2 that refers to a cofactor that "has a stereo-specificity similar to." If to the contrary, examiner kindly requests that Applicants provide a specific location in the disclosure of the phrases at issue.

Written Description Rejection

In claims 1, 4, 5, and 29, Applicants refer to "an alpha-lactalbumin fragment of SEQ ID NO:1 or SEQ ID NO:2 that comprises at least 100 amino acids in length" and in claims 6 and 30, Applicants refer to "an alpha-lactalbumin variant in which the calcium binding site has been modified." All dependent claims are included in this rejection because they depend from rejected base claims 1 and 29 and do not cure the deficiency of the base claims. Therefore the structures of the variants do not correspond with their function.

A representative number of species means that the species which are adequately described are representative of the entire genus. The written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus, i.e. any fragment of SEQ ID NO:1 or SEQ ID NO:2 that comprises at least 100 amino acids in length or any variant of lactalbumin where the calcium binding site has been modified. The claimed genus of those variants could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed polypeptides encompasses widely variant species. Therefore, based on the unlimited variations contemplated, one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional. *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at

page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons above, the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants responded that one of the ordinary skilled in the art will concluded that the Applicants had possession of the claimed fragments and that a fragment of at least 100 amino acids containing SEQ ID NO:1 or SEQ ID NO:2 would retain the required function and that those fragments could be reasonably identified from the alignments available in the art. Further, Applicants state that the alpha lactalbumin sequences from multiple species are highly homologous, and present a publication by Watanabe M. that addresses multiple species of alpha-lactalbumin. In addition, Applicants argue that one skilled din the art would be able to make different variants and fragments of alpha-lactalbumin.

Examiner acknowledges Applicants' arguments however finds them unpersuasive because the claims as presented do not have a nexus between the structure of potential variants and their function, since a fragment of SEQ ID NO:1 or

SEQ ID NO:2 that comprises at least 100 amino acids in length can have distinct structure than the full length of the SEQ ID NO:1 or SEQ ID NO:2, and thus the fragments/variants can have distinct function. Therefore, the written description requirement is not satisfied.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 13, 14, 18, 19, 20, 23, and 26-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Swensson et al., Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis, PNAS (April 11, 2000), vol.97, no.8, p. 4221-4226.

Swensson et al. on pages 4223-4, teach that the conversion of α-lactalbumin to the apoptosis-inducing form involved a cofactor from casein; where α-lactalbumin was converted from the regular, native state to a folding variant with altered biological function, where conversion to HAMLET (human α-lactalbumin made lethal to tumor cells) required partial unfolding of the protein and a specific fatty acid, C18:1, as a necessary cofactor (instant claims 1, 2, 3, 5, 18, 19, 23, 27-29, where the fatty acids would not necessary only include C18:1:9 since the structure of the fatty acid is similar

to C18:1 as in the amended claims; claims 1 and 29 are included in this rejection because Applicants refer to human lactalbumin that is known in the art or claim fragments of lactalbumin or a variants of SEQ ID NO:1 or SEQ ID NO:2 that are least 100 amino acids in length). See pages 4223-4; Figures 1-3 and Abstract. Also, on page 4225, *Discussion* section, the conformation of HAMLET was achieved by changing the conformation of α-lactalbumin from the native to a partially unfolded state by using EDTA treatment because it releases the calcium ions (instant claims 13, 14, 30). (This reference would apply to claims 1, 2, 18, 19, 26-29 of the instant invention, because C18:1 fatty acid could be represented by C18:1:11 or C18:1:9). α-lactalbumin from human milk whey and recombinant protein was shown to convert to the active complex only on the C:18:1 fatty acid-preconditioned column and only when applied in the apo form. See page 4224) bottom right paragraph.

Claim 13 is included in this rejection because it states that the complex further comprises calcium atoms. Swensson et al. state that the binding of calcium is reduced or that calcium ions are released from the configuration, but the reference never excludes completely calcium ions that could be present in the complex.

Claim 14 is included in this rejection because a pharmaceutically acceptable carrier could be water or a buffer solution, for example.

Applicants responded that the claims as presented overcome the rejections since only oleic acid is included in the reference as C18:1:9. Examiner respectfully disagrees and states that the claims as presented refer to fatty acids that have configuration

similar to C18:1 and that have a stereo-specificity that is similar to C18:1, and therefore the rejection still applies.

Claims 1-5, 13, 14, 18, 19, and 26-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Hakansson et al., A folding variant of α-latalbumin with bactericidal activity against Streptococcus pneumoniae, Molecular Biology, 2000, 35(3), pages 589-600.

Hakansson et al. teach α-latalbumin folding variant where the native α-latalbumin could be converted to the active form in the presence of cofactor C18:1 fatty acid. See Abstract. On page 562, Table 2, shows protein folding variants of α-latalbumin where different fatty acids were used: oleic acid (C18:1), stearic acid (C18:0) and palmitic acid (C16:0) and on page 595, left paragraph, it is taught that α-latalbumin from human milk whey was activated by cofactor as a C18:1 fatty acid.. (Instant claims 1-5, 13, 14, 18, 19, and 26-30, since the cofactor can have similar structure or similar configuration to the fatty acids disclosed in the prior art).

On pages 595, right column, and page 596, left column, it is taught that the well known native form of α-latalbumin has affinity to calcium, where the calcium binding cite is co-ordinated by the side chain carboxylates As-82, Asp-87 and Asp 88p; where the calcium ion the molecule changes the conformation to the apo-form (instant claims 13, 14, 30).

Therefore, the aforementioned rejected claims are anticipated by Hakansson et al. because the structure α-lactalbumin is known in the art and a complex of the

lactalbumin and calcium is activated by fatty acids such as C18:1 or that have structure similar to C18:1 or others as disclosed by the prior art.

Applicants responded that because they amended the claims the art is overcome since the prior art only teaches C18:1.

Examiner respectfully disagrees and states that claims as amended refer to fatty acid structures that are similar to C18:1:9 or have stereospecificity that is similar to C18:1:9, and therefore would encompass different fatty acids claimed in the instant invention and presented in the prior art. Therefore the rejections stands and it is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-8, 29, 31, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swensson et al., Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis, PNAS (April 11, 2000), vol.97, no.8, p. 4221-4226 in view of Permyakov et al., Mutating aspartate in the calcium-binding site of α-latalbumin: effects on the protein stability and cation binding, Protein Engineering, vol.14, No.10, pp. 785-789, 2001.

The teachings of Swensson et al. are disclosed above. Swensson et al. does not teach mutations in α-lactalbumin.

Permyakov et al. teach measurements of Ca(II) affinity of mutants of α-lactalbumin, where mutants D87A and D87Nα-lactalbumin are unable to bind calcium ions. See page 785, middle of the right paragraph. (instant claims 1, 6, 7, 8)

On page 786, recombinant proteins D87A and D87Nalpha-lactalbumin were expressed in E.coli, and as a consequence of protein expression, the recombinant protein contained extra methionine residue on N-terminus, which is known to destabilize α-lactalbumin; and where α-lactalbumin with D87 N mutation was unable to fold properly or bind calcium ions (claims 7, 8, 29, 31, 32 of the instant invention).

Therefore, it would have been obvious to one of an ordinary skilled in the art at the time the invention was made to design a mutated α-lactalbumin where calcium binding site has been modified, so that the affinity for calcium is reduced as taught by Permyakov et al. and combine these with teachings of Swensson et al. that teach a composition of α-lactalbumin and a cofactor with altered calcium binding ability.

Applicants responded that there is no motivation to combine these references and that there is no expectation of success.

Examiner respectfully disagrees and states that those two references clearly provide a motivation to design a mutated lactalbumin where the calcium binding site is modified so the affinity of calcium is reduced, for example. Further, those two references clearly show the composition of lactalbumin and a cofactor with altered binding affinity. Therefore, the rejection stands.

Conclusion

No claims are allowed.

Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. Should you have

any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

Karen Cochrane Carlson PhD

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PRIMARY EXAMINER